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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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LISA A. HAILE, PH.D.
GRAY CARY WARE & FREIDENRICH LLP
4365 EXECUTIVE DRIVE
SUITE 1600
SAN DIEGO, CA 92121-2189

EXAMINER	
BECKERLEG, ANNE M	

ART UNIT	PAPER NUMBER
1632	15

DATE MAILED: 03/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/225,904	SIDRANSKY ET AL.
	Examiner	Art Unit
	Anne M Beckerleg	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-9 and 12-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-9 and 12-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachments

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other

DETAILED ACTION

Continued Prosecution Application

The request filed on 1/10/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/225,904 is acceptable and a CPA has been established. Applicant's amendment filed with the CPA request on 1/10/02 has also been entered. Claims 2-6, 10 and 11 have been canceled. New claims 12-33 have been added. Claims 1, 7-9, and 12-33 are pending in the instant application. Please note that the both the art unit and the examiner of record in the instant application have changed, see page 10. An action on the CPA follows.

The text of those sections of Title 35, US code, not included in this action can be found in previous office actions.

Claim Rejections - 35 USC § 112

The rejection of claims 1-3, 5, and 7-11 under 35 U.S.C. 112, second paragraph, has been

The rejection of claims 1-11 under 35 U.S.C. 112, first paragraph, for lack of enablement, is maintained in modified form over pending claims 1, 7-9, and new claims 12-33. The rejection of claims 2-6, and 10-11 is withdrawn in view of the cancellation of these claims. Applicant's arguments as they pertain to the instant rejection of the claims have been fully considered but have not been found persuasive in overcoming the rejection for reasons discussed in detail below.

The applicant's claims as amended or newly added recite methods of treating malignant cell proliferative disorders associated with altered p16 expression or with decreased expression of a 5' ALT polynucleotide or polypeptide comprising the administering a polynucleotide encoding a 5'ALT polypeptide. The specification discloses that a 5'ALT polypeptide refers to polypeptides translated from alternative splice variants derived from mRNA transcribed from the p15/p16 genes which contain a 5'ALT exon.

The specification does not provide sufficient guidance for inhibiting the proliferation of any and all types of tumors which exhibit decreased expression of 5' ALT or p16, or which express mutant 5 'ALT or p16 by administration of any expression construct encoding a 5' ALT. The claims as written are extremely broad and read on any polypeptide which contains the 5'ALT exon identified in the specification. The specification does not teach or provide any evidence that the 5'ALT exon by itself has any biological activity or that the attachment of the 5'ALT exon to any other gene sequence results in the expression of a protein with any anti-tumor activity. The

regards to these transcripts, while the specification does demonstrate the existence of these alternative transcripts in cells, the specification provides no evidence that these transcripts actually produce protein *in vivo* or that the protein produced has any particular biological activity. The working examples provided only demonstrate the *in vitro* translation of these alternative transcripts. The working examples do not demonstrate that the protein products produced from 5' ALT /$p16^{INK4A}$ or 5' ALT/$p15^{INK4B}$ share any of the known activities of either wild type p16 or p15. In addition, the specification fails to provide any evidence which correlates either the lack of 5' ALT /$p16^{INK4A}$ or 5' ALT/$p15^{INK4B}$ expression or the expression of mutant forms of 5' ALT /$p16^{INK4A}$ or 5' ALT/$p15^{INK4B}$ in a cell with the generation of a malignant hyperproliferative state such that there might exist an expectation that expression of 5' ALT /$p16^{INK4A}$ or 5' ALT/$p15^{INK4B}$ would reverse that phenotype. In regards to tumor cells with known mutations, deletions, or hypermethylation of p16, it is again noted that the specification has not provided any evidence that a protein translated from a 5' ALT transcript shares any of the known activities of p16.

Furthermore, at the time of filing, the art recognized that the regulation of cell growth is a complex process involving numerous inter- and intracellular interactions. Disregulation of this process through genetic mutation results in neoplasia. As Vogelstein et al. explains, " each individual cancer arises not from a single mutation, but from the accumulation of several mutations" (Vogelstein et al. (1993) Trends in Genetics, Vol. 9(4), page 138, lines 9-11). A corollary to this principle is that [illegible]

transformed cells, mutations in tumor suppressor genes, and mutations in oncogenes. Vogelstein et al. teach that while the mutation of the abl oncogene to c-abl can be found in many chronic myelogenous leukemias, mutations in the tumor suppressor gene APC are more common in colorectal tumors (Vogelstein et al. (1993) Trends in Genetics, Vol. 9(4), page 140, column 2, paragraphs 2-3, and page 141, column 1, paragraphs 1-2). Thus, successful use of the instant invention for the treatment of a particular tumor would require detailed knowledge of the genetic mutations of a particular type of tumor in order to specifically counteract the growth promoting effects of the transforming mutations. In addition, individual transformed cells of a tumor acquire new mutations over time, resulting in clonal subsets with differential sensitivities to drugs, radiation, and immune attack (Vogelstein et al. (1993) Trends in Genetics, Vol. 9(4), page 141, column 1, paragraph 1). Therefore, in view of the complex pattern of mutations that results in the generation of a malignant hyperproliferative cell, the skilled artisan would not have been able to predict in the absence of specific evidence whether the correct of a single mutation in a malignant cell would result in the reversal of the hyperproliferative phenotype.

The applicant's specification further does not provide sufficient guidance for inhibiting the proliferation of tumors *in vivo* in any and all animals using any DNA expression construct encoding a 5' ALT polynucleotide and using any route of administration. The specification discloses that both viral and non-viral vectors can be used to express the 5' ALT polynucleotide, including [illegible] vectors. Further, the specification reads broadly on the

intraperitoneal. The specification fails to provide any guidance as to the level of 5' ALT polypeptide expression that correlates with decreased tumor growth in any type of malignant hyperproliferative cell. Further, the specification does not provide guidance that systemic injection of a 5' ALT polypeptide or injection at any location including the tumor itself can result in a therapeutic level of 5' ALT polypeptide expression such that a therapeutic effect on the tumor is observed. As wild type p16 protein functions by directly affecting cell cycle progression, it would appear to be essential that the 5' ALT construct transfect/infect and express 5' ALT in the tumor cells themselves. While the specification discusses several strategies to target vectors to certain cellular receptors, the specification does not provide sufficient guidance as to the nature of cellular receptors found on all cancer cells, teach specific receptors found on prostate cancer cells or neuroblastomas, or demonstrate the targeted transfection or infection of tumor cells resulting in a therapeutic effect on the tumor.

In addition, at the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells and getting them expressed remain a

therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1). Orkin et al. further states in a report to the NIH that, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2). Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, particularly against adenoviral proteins, and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, " .. the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

provided by the specification for the parameters affecting delivery and expression of therapeutic amounts of 5' ALT in tumor cells in a mammal as discussed above, the lack of guidance concerning the biological activities of any 5' ALT polypeptide, the lack of working examples, and the breadth of the claims, it would have required undue experimentation to practice the instant invention and the skilled artisan would not have predicted success in treating or inhibiting any and all tumor growth using any 5' ALT encoding vector and any route of delivery.

In response to the previous rejection of record, the applicant argues that Stolberg et al., submitted with a prior response, demonstrates that gene therapy can be effective for treating specific disorders associated with aberrant expression of specific genes and that therefore the skill artisan would have predicted success in using the claimed methods for treating tumors having the recited characteristics. As stated in previous office actions, Stolberg in fact teaches the difficult hurdles that need to be overcome in order to successfully treat a particular disease where the disease mechanism is well known. For example, Stolberg teaches that "scientists have had trouble devising delivery vehicles, called vectors, that can direct genes into the proper cells and get them to function once they are there". Thus, Stolberg agrees with the teachings of Verma et al., Orkin et al. and Marshall et al. cited above that gene therapy of disease using recombinant vectors is unpredictable. Furthermore, in the instant case, the specification has failed to establish a nexus between the 5' ALT mutations or lack of expression of 5' ALT and the generation of malignant [illegible]. In addition, the specification fails to demonstrate that 5' ALT

The applicants have also resubmitted a post-filing reference by Liggett et al. as evidence that the claimed methods are enabled for the treatment of tumors. The Liggett et al. reference describes *in vitro* experiments involving the transfection of squamous cell carcinomas with a plasmid encoding a p16β splice variant. The reference makes no mention of a 5'ALT transcript, however, it is noted that the applicant has stated that p16β is 5' ALT-l6. Liggett et al. demonstrates that expression of p16β results in decreased survival of tumors cell lines *in vitro* with mutations in p16 or p16β. While these results provide an indication that p16β expression can affect the rate of growth of a tumor cell with a mutation in p16 or p16β, they provide no guidance for the actual treatment of tumors *in vivo*. Liggett et al. does not teach any routes of *in vivo* vector delivery, levels of p16β expression *in vivo*, vectors other than a plasmid vector encoding p16β, or 5'ALT polypeptides other than p16β. Thus, the results presented by Liggett et al. are not commensurate in scope with the instant claims and further fail to provide a nexus between the disclosed *in vitro* assays and the instant methods of treating tumors *in vivo*. Finally, the applicant is reminded that 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970). Furthermore, "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166

No Claims are allowed.

The claims are free of the prior art of record, as the prior art of record does not teach or suggest the treatment of cancer *in vivo* using an alternative splice variant of p16 or p15.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Beckerleg

A.M.S. BECKERLEG
PATENT EXAMINER